MULTIFUNCTIONAL ORGANIC POLYMERS

This is a continuation in part of U.S. Ser. No. 07/740,703, entitled "Biocompatible Microcapsules," filed Aug. 5, 1991, by Jeffrey A. Hubell, and Amarpreet S. Sawhney, which is a divisional of U.S. Ser. No. 07/598,880 filed Oct. 15, 1990, now issued as U.S. Pat. No. 5,232,984.

BACKGROUND OF THE INVENTION

This invention is generally in the area of organic polymer chemistry, specifically multifunctional polymers.

Cell adhesion plays an important role in human disease. These interactions proceed by the interaction of receptors upon the surface of a cell with proteins or glycosaminoglycans upon the surface of another cell or within the extracellular matrix. These receptors may be proteins or glycosaminoglycans.

Routes to the interruption of these interactions typically involve competitive inhibition of these receptor-ligand interactions, for example, with antibodies (e.g., anti-glycoprotein IIb/IIIa complex for anti-platelet therapy), soluble ligands which act as receptor antagonists (e.g., cyclic RGD peptides or von Willebrand factor fragments), soluble receptors, or other competitors.

It has also recently been demonstrated that it is possible to inhibit these interactions by mechanical means, for example, by photopolymerizing poly(ethylene glycol)-based hydrogels upon the cell, cell aggregate, matrix or tissue.

An example of the use of hydrogels to inhibit tissue adhesion is described by U.S. Pat. No. 5,126,141 to Henry. The process utilizes thermo-reversible gels of mixtures of polyoxyalkylene polymers and ionic polysaccharides applied to the tissues as liquids.

Unfortunately, the inhibitor based methods have a disadvantage common to many drug therapies, in that it is difficult to restrict the activity of the inhibitors to the region of interest. Hydrogel barriers are difficult to place and it is difficult to control chemical processes associated with them.

Isolated cells or tissues have also been protected from cell-cell contact, in this case from attack by immune cells, by placement within microcapsules formed of water soluble non-ionic polymers such as polyethylene oxide grafted to polycationic polymers such as poly-L-lysine. However, this is restricted to the use of isolated cells or tissues which are encapsulated within the polymer at the time of polymerization for subsequent implantation into the body.

It is therefore an object of the present invention to provide methods for making and using compositions, and the resulting compositions, for inhibiting tissue adhesion and cell-cell contact within the body.

It is a further object of the present invention to provide methods for making multifunctional polymeric materials which can be biodegradable and which can be used for drug delivery, either at a specific tissue-polymeric material interface or as a result of release of bioactive agents during degradation of polymeric material.

SUMMARY OF THE INVENTION

A bi-functional polymeric material for use in inhibiting cell-cell contact and tissue adhesion is disclosed wherein one domain of the material (i.e., one region with a particular function) is a polymer which adsorbs to cells or tissue (referred to collectively below as "tissue"), and the other domain of the polymeric material is a polymer which does not adsorb to tissue. Since most tissues bear a net negative charge, a positively charged polymer (polycation) is used as the tissue-binding domain. A water-soluble polymer that does not bear charge (polynonion) is used as the non-binding domain. When the two-domain polymeric material contacts a tissue, the tissue-binding domain(s) binds and immobilizes the attached non-binding domain(s), which then generally extends away from the tissue surface and sterically blocks the attachment of other tissues.

Additional domains, linking groups, and bioactive materials can be added to this basic two-domain structure to confer, for example, adhesion to particular types of cells or molecules or degradation by enzymatic or non-enzymatic means. These domains may be a third type of polymer, or when serving to direct attachment, a peptide such as RGD, or even a single amino acid, which is used to target a polyamino acid for cleavage by an enzyme.

The polymer is applied in a fluid phase to the tissues or cells to be protected, whereupon the tissue binding domains adsorb the polymeric material to the tissue. The fluid phase can be applied to isolated tissue or to tissue during surgery or by means of a catheter or other less invasive device.

The compositions are useful for blocking adhesion and immune recognition and thus may be useful in the treatment of many diseases, including the prevention of postoperative adhesions, protecting injured blood vessels from thrombosis and intimal thickening relating to restenosis, and decreasing the extent of metastasis of tumor cells in tissues.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic illustration of the interaction between a two domain polymeric material and cells or tissue which has been treated with the polymeric material to decrease adhesiveness.

FIGS. 2*a* and 2*b* are photographs of a rat carotid artery 24 hours after crush injury without treatment (FIG. 2*a*) and treated with a 5% solution of PEG-b-PLL for two minutes (FIG. 2*b*).

DETAILED DESCRIPTION OF THE INVENTION

I. General Structures of the Polymers.

There are three general structures of the polymeric materials described herein. Each structure is a block copolymer, i.e., a polymer composed of connecting multiple polymer chains of different composition. The three structures are (1) brush copolymers (as in a bottle brush, with a backbone of one composition and bristles of another) with a backbone of poly(B) and bristles composed of poly(A), (A)x-b-(B)y; (2)AB block copolymers, i.e., (A)x(B)y, or a poly(A) connected at one end to a poly (B); and (3) ABA block copolymers, i.e., (A)x(B)y(A)z, or a poly(A) connected at both ends to poly(A) chains, or in a less preferred embodiment, (B)x(A)y(B)z; where A is a monomer, the polymer of which does not bind strongly to a tissue; B is a monomer, the polymer of which does bind strongly to a tissue; x is an integer of greater than or equal to 5; y is an integer of greater than or equal to 3; and z is an integer greater than or equal to zero. As used herein, "polymeric materials" include polymers of oligomers. X is determined as that number providing the desired degree of repulsiveness or non-adhesiveness to tissue; y is determined as that number providing the desired degree of adhesiveness of the polymeric material to tissues, as discussed in more detail below. Poly(A) and poly(B) are generally linear polymers, although both may be linear or branched. Both A and B can be monomers, mac-